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*164342 Nucleotide, Related Entries, Protein, PubMed, LinkOut

OLFACTORY RECEPTOR, FAMILY 1, SUBFAMILY D, MEMBER 2; OR1D2

Alternative titles; symbols

OLFACTORY RECEPTOR 1; OLFR1

Gene map locus 17p13.3

TEXT

The olfactory system is able to distinguish several thousand odorant molecules. Olfactory receptors are believed to be encoded by an extremely large subfamily of G protein-coupled receptors. These receptors share a 7-transmembrane domain structure with many neurotransmitter and hormone receptors. They are responsible for the recognition and G protein-mediated transduction of odorant signals. The genes encoding these receptors are devoid of introns within their coding regions, but have a long intron splicing the 5-prime untranslated region. Schurmans et al. (1993) cloned a member of this family of genes, OLFR1, from a genomic library by cross-hybridization with a gene fragment obtained by PCR. By isotopic in situ hybridization, they mapped the gene to 17p13-p12 with a peak at band 17p13. A minor peak was detected on chromosome 3, with a maximum in the region 3q13-q21. After MspI digestion, a RFLP was demonstrated. Using this in a study of 3 CEPH pedigrees, they demonstrated linkage with D17S126 at 17pter-p12; maximum lod = 3.6 at theta = 0.0. Used as a probe on Southern blots under moderately stringent conditions, the cDNA hybridized to at least 3 closely related genes. Ben-Arie et al. (1994) cloned 16 human OLFR genes, all from 17p13.3. The intronless coding regions are mapped to a 350-kb contiguous cluster, with an average intergenic separation of 15 kb. The OLFR genes in the cluster belong to 4 different gene subfamilies, displaying as much sequence variability as any randomly selected group of OLFRs. This suggested that the cluster may be one of several copies of an ancestral OLFR gene repertoire whose existence may have predated the divergence of mammals. Localization to 17p13.3 was performed by fluorescence in situ hybridization as well as by somatic cell hybrid mapping.

The ability to distinguish different odors depends on a large number of different odorant receptors (ORs). Sullivan et al. (1996) noted that ORs are expressed by nasal olfactory sensory neurons; each neuron expresses only 1 allele of a single OR gene. In the nose, different sets of ORs are expressed in distinct spatial zones. Neurons that express the same OR gene are located in the same zone; however, in that zone they are randomly interspersed with neurons expressing other ORs. This distribution suggested to the authors that, when the cell chooses an OR gene for expression, it may be restricted to a specific zonal gene set, but it may select from that set by a stochastic mechanism. Proposed models of OR gene choice fall into 2 classes: locus-dependent and locus-independent. Locus-dependent models posit that OR genes are clustered in the genome, perhaps with members of different zonal gene sets clustered at

distinct loci. In contrast, locus-independent models do not require that OR genes be clustered. To assess the feasibility of these models, Sullivan et al. (1996) determined the expression zones, sequences, and chromosomal locations of a number of mouse OR genes. They mapped OR genes to 11 different regions on 7 chromosomes. These loci lie within paralogous chromosomal regions that appear to have arisen by duplications of large chromosomal domains followed by extensive gene duplication and divergence. These studies showed that OR genes expressed in the same zone map to numerous loci; moreover, a single locus can contain genes expressed in different zones. These findings raised the possibility that OR gene choice is locus-independent or involved consecutive stochastic choices.

Nekrasova et al. (1996) overexpressed human (OR17-4) and rat (olp4) olfactory receptor genes in insect cells, purified them, and characterized them biochemically. They identified monomeric, dimeric, and trimeric forms of the proteins corresponding to molecular weights of 32, 69, and 94 kD by electrophoresis. The oligomers were resistant to reduction and alkylation and were therefore thought to be held together by SDS-resistant hydrophobic interactions, consistent with observations of other G protein-coupled receptors.

Glusman et al. (1996) described the results of complete sequencing of an OR-rich cosmid spanning the center of the OR gene cluster on 17p13.3. The resulting 40-kb sequence revealed 3 known OR coding regions, 2 OR genes which may have originated from a tandem duplication event, and a new OR pseudogene fused to another OR gene.

Issel-Tarver and Rine (1996) characterized 4 members of the canine olfactory receptor gene family. The 4 subfamilies comprised genes expressed exclusively in olfactory epithelium. Analysis of large DNA fragments using Southern blots of pulsed field gels indicated that subfamily members were clustered together, and that 2 of the subfamilies were closely linked in the dog genome. Analysis of the 4 olfactory receptor gene subfamilies in 26 breeds of dog provided evidence that the number of genes per subfamily was stable in spite of differential selection on the basis of olfactory acuity in scent hounds, sight hounds, and toy breeds.

Issel-Tarver and Rine (1997) performed a comparative study of 4 subfamilies of olfactory receptor genes first identified in the dog to assess changes in the gene family during mammalian evolution, and to begin linking the dog genetic map to that of humans. These 4 families were designated by them OLF1, OLF2, OLF3, and OLF4 in the canine genome. The subfamilies represented by these 4 genes range in size from 2 to 20 genes. They are all expressed in canine olfactory epithelium but were not detectably expressed in canine lung, liver, ovary, spleen, testis, or tongue. The OLF1 and OLF2 subfamilies are tightly linked in the dog genome and also in the human genome. The smallest family is represented by the canine OLF1 gene. Using dog gene probes individually to hybridize to Southern blots of genomic DNA from 24 somatic cell hybrid lines. They showed that the human homologous OLF1 subfamily maps to human chromosome 11. The human gene with the strongest similarity to the canine OLF2 gene also mapped to chromosome 11. Both members of the human subfamily that hybridized to canine OLF3 were located on chromosome 7. It was difficult to determine to which chromosome or chromosomes the human genes that hybridized to the canine OLF4 probe mapped. This subfamily is large in mouse and hamster as well as human, so the rodent background largely obscured the human cross-hybridizing bands. It was possible, however, to discern some human-specific bands in blots corresponding to human chromosome 19. They refined the mapping of the human OLF1 homolog by hybridization to YACs that map to 11q11. In dogs, the OLF1 and OLF2 subfamilies are within 45 kb of one another (Issel-Tarver and Rine (1996)). Issel-Tarver and Rine (1997) demonstrated that in the human OLF1 and OLF2 homologs are likewise closely linked. By studying YACs, Issel-Tarver and Rine (1997) found that the human OLF3 homolog maps to 7q35. A chromosome 19-specific cosmid library was screened by hybridization with the canine OLF4 gene probe, and clones that hybridized strongly to the probe even at high stringency

were localized to 19p13.1 and 19p13.2. These clones accounted, however, for a small fraction of the homologous human bands.

Rouquier et al. (1998) demonstrated that members of the olfactory receptor gene family are distributed on all but a few human chromosomes. Through fluorescence in situ hybridization analysis, they showed that OR sequences reside at more than 25 locations in the human genome. Their distribution was biased for terminal bands of chromosome arms. Flow-sorted chromosomes were used to isolate 87 OR sequences derived from 16 chromosomes. Their sequence relationships indicated the inter- and intrachromosomal duplications responsible for OR family expansion. Rouquier et al. (1998) determined that the human genome has accumulated a striking number of dysfunctional copies: 72% of these sequences were found to be pseudogenes. ORF-containing sequences predominate on chromosomes 7, 16, and 17.

Trask et al. (1998) characterized a subtelomeric DNA duplication that provided insight into the variability, complexity, and evolutionary history of that unusual region of the human genome, the telomere. Using a DNA segment cloned from chromosome 19, they demonstrated that the blocks of DNA sequence shared by different chromosomes can be very large and highly similar. Three chromosomes appeared to have contained the sequence before humans migrated around the world. In contrast to its multicopy distribution in humans, this subtelomeric block maps predominantly to a single locus in chimpanzee and gorilla, that site being nonorthologous to any of the locations in the human genome. Three new members of the olfactory receptor (OR) gene family were found to be duplicated within this large segment of DNA, which was found to be present at 3q, 15q, and 19p in each of 45 unrelated humans sampled from various populations. From its sequence, one of the OR genes in this duplicated block appeared to be potentially functional. The findings raised the possibility that functional diversity in the OR family is generated in part through duplications and interchromosomal rearrangements of the DNA near human telomeres.

Mombaerts (1999) reviewed the molecular biology of the odorant receptor genes in vertebrates. Buck and Axel (1991) discovered this large family of genes encoding putative odorant receptor genes. Zhao et al. (1998) provided functional proof that one OR gene encodes a receptor for odorants. The isolation of OR genes from the rat by Buck and Axel (1991) was based on 3 assumptions. First, ORs are likely G protein-coupled receptors, which characteristically are 7-transmembrane proteins. Second, ORs are likely members of a multigene family of considerable size, because an immense number of chemicals with vastly different structures can be detected and discriminated by the vertebrate olfactory system. Third, ORs are likely expressed selectively in olfactory sensory neurons. Ben-Arie et al. (1994) focused attention on a cluster of human OR genes on 17p, to which the first human OR gene, OR1D2, had been mapped by Schurmans et al. (1993). According to Mombaerts (1999), the sequences of more than 150 human OR clones had been reported. The human OR genes differ markedly from their counterparts in other species by their high frequency of pseudogenes, except the testicular OR genes. Research showed that individual olfactory sensory neurons express a small subset of the OR repertoire. In rat and mouse, axons of neurons expressing the same OR converge onto defined glomeruli in the olfactory bulb.

Gilad et al. (2000) reported the population sequence diversity of genomic segments within a 450-kb cluster of olfactory receptor genes on chromosome 17. They found a dichotomy in the pattern of nucleotide diversity between OR pseudogenes and introns on the one hand and the closely interspersed intact genes on the other. They suggested that weak positive selection is responsible for the observed patterns of genetic variation. This was inferred from a lower ratio of polymorphism to divergence in genes compared with pseudogenes or introns, high nonsynonymous substitution rates in OR genes, and a small but significant overall reduction in variability in the entire OR gene cluster compared with other genomic regions. The dichotomy among functionally distinct segments within a short genomic distance

requires high recombination rates within this OR cluster.

Olfactory receptor genes are organized in the mammalian genome in many clusters. The cluster on 17p13.3, fully sequenced by Glusman et al. (2000), includes 17 OR genes out of the expected several hundred in the human olfactory subgenome. The OR genes in this cluster belong to various families and subfamilies. Conversely, genes from the same family have been found in different clusters and on different chromosomes (Sullivan et al., 1996; Rouquier et al., 1998), suggesting a complex history of gene and cluster duplications. By 'data mining,' Glusman et al. (2000) identified 831 OR coding regions (including pseudogenes) in 24 vertebrate species. A nomenclature system for the OR gene superfamily was proposed, based on a divergence evolutionary model.

Fuchs et al. (2001), who referred to the repertoire of olfactory receptor genes as the olfactory subgenome, analyzed 224 such genes derived by a literature survey, data mining at 14 genomic clusters, and an OR-targeted experimental sequencing strategy. This set of genes contained at least 53% pseudogenes and was minimally divided into 11 gene families. One family has undergone a particularly extensive expansion in primates.

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